DEPARTMENT OF HEALTH AND HUMAN SERVICES **510k Memo**

Division of General and Restorative, and Neurological Devices
General Surgery Devices Branch, HFZ-410
(301) 594-2037

Food and Drug Administration
Office of Device Evaluation
Center for Devices and Radiological Health
9200 Corporate Boulevard
Rockville, MD 20850

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To: Richard Felten, Neil Ogden, The file
From: Michael J Schlosser, M.D., Medical Officer
Subject: Concentric Retriever Clinical consult

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Clinical Background: The efficacy of thrombolytic therapy for acute ischemic stroke is based on the restoration of blood flow to neurons within the ischemic penumbra. The ischemic penumbra is a population of viable neurons within a region of cerebral ischemia. These neurons are stunned by limited blood flow, but can be salvaged by restoration of flow within a time limit. Intravenous tissue-type plasminogen activator (tPA) has been shown to improve the outcome of acute ischemic stroke when given within the first 3 hours after onset of symptoms (4). Other trials have failed to show an overall benefit when the treatment window was extended to 6 hours (5, 7). While the PROACT I and II studies did support an overall benefit of intra-arterial tPA given within 6 hours of symptom onset, the drug was not approved by the FDA for this indication (1, 6). As such, the only currently approved treatment for acute stroke remains IV tPA. Due to the short time window, numerous contraindications, and risk of intracranial hemorrhage (ICH), on average only 2% of patients suffering from acute stroke receive this therapy.

Mechanical thrombectomy holds the promise of restoration of blood flow to ischemic brain while limiting the risk of intracranial hemorrhage (8). It also can be employed in patients with conditions that make them poor candidates for IV or IA tPA. The success of thrombolytic therapy is limited by the size of the clot. Evidence has shown that cohorts of patients presenting with smaller, more distal occlusions fare better with thrombolytic therapy than those with larger more proximal lesions. Mechanical thrombectomy may allow the treatment of patients with larger clots in more proximal arteries.

The Concentric Retriever is already legally marketed as a tool for retrieving foreign bodies from the peripheral and neurovasculature. In order to demonstrate the safety and efficacy of the device for removing thrombus from the neurovasculature, a single-armed study was deemed appropriate. This study would use the surrogate endpoint of successful revascularization (evidenced by achieving TIMI II or III flow) as its measure of efficacy. This was believed to be an appropriate surrogate endpoint to demonstrate the effectiveness of this device for the proposed indication because the NINDS stroke trial, the PROACT studies, as well as subsequent studies of thrombolytics published in the literature have provided some indication that revascularization of ischemic cortex improves clinical outcome. At a previous meeting of the FDA Neurological Devices advisory panel, the panel recommended that devices indicated for treatment of stroke be studied in a randomized, controlled trial with neurological improvement as the primary

endpoint. FDA agrees with this recommendation in general, however, we believe this device, indicated for removal of thrombus, may be appropriately labeled as a tool for assisting neurointerventionalists in managing patients with acute stroke.

Device Description: The Concentric Retriever consists of a nitinol wire with a helical shaped tip. The device is intended for retrieval of thrombus within the neurovasculature in patients suffering from ischemic stroke. The wire is passed through the thrombus within a microcatheter. Once the microcatheter is beyond the occlusion, the catheter is retracted and the wire within reforms the helical shape. The catheter and the retriever are then pulled back to engage the thrombus. At this point the entire apparatus is retracted back into the balloon guide catheter, bringing the thrombus with it. The thrombus and guide catheter can then be removed from the patient.

Description of Clinical Protocol:
Trial design: Prospective, multi-center, non-randomized, single arm trial of 125 patients presenting with acute ischemic stroke. As this was a single arm trial design, there was no control population prospectively studied. Results were to be compared with the placebo group in the PROACT II trial (1).

Patient population: The Patient population included individuals = 18 years of age who presented with clinical symptoms suggestive of an acute ischemic stroke. Patients were considered for enrolment if they presented within 3 hours of symptom onset, but were not a candidate (i.e. they possess one of the absolute contraindications) for thrombolytic therapy. Alternatively, patients who presented after 3 hours, and in whom the thrombectomy procedure could be completed before 8 hours after symptom onset were also included. Only patients with a presenting National Institute of Health Stroke Scale (NIHSS) score of = 8 and who signed informed consent were enrolled. Patients who met these criteria received a selective cerebral angiogram. Patients with occlusion (TIMI grade 0 or I flow) in the M1 or M2 segments of the middle cerebral artery (MCA), internal carotid artery (ICA), basilar or vertebral arteries were included in the study.

Exclusion criteria:

1) pregnant
2) Blood glucose < 50.
3) Arterial tortuosity that would prevent the device for reaching the target.
4) Hemorrhagic diathesis, coagulation factor deficiency, or INR > 3.0.
5) PTT > 2 time normal within the past 48 hours.
6) Platelet count < 30,000
7) Severe allergy to IV contrast dye.
8) Uncontrolled hypertension (systolic blood pressure > 185 or diastolic > 110)
9) CT or MRI scan reveals mass effect
10) Arterial stenosis > 50% proximal to the occlusion
11) Life expectancy is < 3 months.
12) Participating in another investigational drug or device study.

Study procedure: Patients presenting with symptoms of acute ischemic stroke were screened by the stroke team to determine potential entry into the study. Patients who met all the inclusion and exclusion criteria were then further assessed and NIHSS, modified Rankin Scale (mRS), Barthel Index (BI), neurological exam and screen blood chemistries obtained. A CT or MRI scan was then obtained (depending on the routine of the treating center) to rule out intracranial hemorrhage or mass effect. Patients who were found not to meet study criteria based on pre-treatment screening were then excluded from the study and the reasons documented. Informed consent was signed prior to catheterization. After completion of informed consent, a selective (anterior or posterior) cerebral angiogram was obtained based on symptoms. Patients who lacked angiographic criteria for entry into the study were then excluded. A patient was not considered enrolled in the study unless the balloon guide catheter was placed.

Once the guide catheter was placed, the microcatheter was then advanced through the identified occlusion and the anatomy distal to the thrombus was studied via another injection through the microcatheter. The Retriever was advanced through the microcatheter and deployed distal to the thrombus. At this point the proximal balloon was inflated to arrest blood flow during the retrieval process. The Retriever was then pulled back to engage the clot. Then, the device and the thrombus were pulled back together into the balloon guide catheter. Up to 6 attempts to retrieve the thrombus were allowed by protocol. After treatment was complete, another angiogram was obtained to document revascularization. Antiplatelet agents could be administered prior to or immediately after the procedure. No anticoagulation was allowed until the 24 hours neuro-imaging was completed.

Outcome measures:
Primary efficacy measure were the achievement of recanalization (TIMI grade II or III flow in all major vessels) immediately post-procedure without occurrence of serious adverse events including vessel perforation or dissection, symptomatic intracranial hemorrhage, or embolization into a previously uninvolved territory.

Secondary endpoint was the measurement of patient's neurologic condition at 30 and 90 days post-procedure. NIHSS, Barthel Index and modified Rankin scale scores will be collected at discharge (or 7 days), 30 and 90 days.

Study success was defined as revascularization rate that is statistically different from the 18% spontaneous revascularization rate seen in the placebo group of the PROACT II trial. Further, the actual rate seen should be greater than 30%.

Patient demographics:

1412 patients presenting with symptoms of acute stroke were screened across 25 centers. From this population, 144 patients were enrolled in the study and 137 were treated. For comparison, in PROACT II, 12,323 patients were screened to treat 180. Complete acute data was available for 121 patients at the time of this submission. Patients were considered enrolled when the balloon guide catheter was inserted into the patient. They

were considered treated when the retriever was deployed into the target vessel. In 7 patients out of the 121 with available data the retriever was not deployed in the target vessel, leaving 114 in the final analysis. Within these 7 patients who were enrolled, but not treated, 1 was excluded due spontaneous recanalization of the vessel prior to treatment, and another due to the occlusion residing in a non-treatable vessel. The remaining 5 were due to an inability to access the occlusion, place the balloon guide or advance the retriever (resulting in a 4% failure to treat rate in patient who met all inclusion and exclusion criteria). Of the 114 patients treated, 65 had occlusions in the MCA, 37 in the ICA or ICA termination and 12 had occlusions in the vertebral or basilar arteries.

The median time from symptom onset to groin puncture was 4.0 hours with a range of 20 minutes to 9.5 hours. The median time to final angiogram was 6.1 hours. The average time from symptom onset to randomization in the PROACT II trial was 5.1 (range of 4.2-5.5) hours for the placebo group and 4.7 (4.0-5.3) hours for the treatment group.

Safety Data:

The protocol for the MERCI trial based success on revascularization while minimizing the rate of 4 serious adverse events: arterial dissection or perforation, symptomatic ICH, or embolization of thrombus into a previously uninvolved territory. Overall, there were 9 cases of symptomatic ICH, 3 cases of arterial perforation, 3 cases of dissection, and 2 cases of embolization into an uninvolved territory. If the patients in whom the perforations lead to a symptomatic hemorrhage are only counted once, the overall number of patients experiencing serious adverse events was 15/114 (13%). These adverse events were individually examined by the investigators and the DSMB to determine if they were device or procedure related, or unlikely to be related to either the device or the procedure. A total of 7 cases were determined to be device or procedure related, serious adverse events (6%).

There were 4 serious adverse events that were determined by the investigators and DSMB to be device-related. Two of these patients experienced contrast extravasation after thrombectomy with the Retriever. This finding was consistent with vessel dissection or perforation. In one case the patient was treated with several other mechanical therapies after unsuccessful treatment with the Retriever. Both of these patients expired. Two additional patients, both with MCA occlusions, experienced embolization of the clot into the ACA territory during attempted thrombectomy resulting in occlusion of the A2 segment. Both of these patients survived. The device-related serious adverse event rate is 3.5% (4/114). One additional patient experienced diffuse SAH and contrast in the subarachnoid space after unsuccessful revascularization. This case was however determined to be procedure and not device-related by the investigator and DSMB.

Procedure related adverse events were seen in 8 cases (7%). These fit the criteria for serious adverse events in three cases. Two of these cases involved dissection of the cervical ICA. In both cases this complication was thought to be due to the placement of the Balloon guide catheter. One of these patients expired due to complications associated with the treatment of the dissection. The other had no sequelae. Another case already

mentioned above involved diffuse SAH that was though to be due to manipulation of a guidewire and not the actual device. Five other patients experienced groin hematomas that were procedure related. Two required surgical evacuation and one a transfusion. No patients with groin hematomas were reported as experiencing any long term impairment as a result of that complication.

There was an overall symptomatic intracranial hemorrhage rate within 24 hours of treatment of 8% (9/114). Hemorrhages were deemed symptomatic if the patient experienced a 4 point or greater decline in NIHSS with the appearance of a hemorrhage on CT scan. Two of these hemorrhages were considered device related (and are including above in the device related adverse events). The hemorrhage rate in patients with MCA occlusions (the population studied in PROACT II) was 6% (4/65). As is expected due to the correlation between increased stroke volume and increased hemorrhage rate, the hemorrhage rate among ICA occlusions in the MERCI trial was higher (14%) than the rate seen for MCA occlusions. Increased baseline NIHSS also corresponds to increase symptomatic ICH. In PROACT II all symptomatic ICH occurred in patients with NIHSS >10, and the rate among patients with NIHSS > 20 was 13%.

Table 1 compares the rates of the most common, serious adverse events for both arms of the PROACT II trial and the MERCI study. Numbers for the patients within the MERCI trial who presented with MCA occlusions are expressed in the footnote. The symptomatic intracranial hemorrhage rate associated with the use of IV tPA to treat stroke is between 6-8% (4,5,7).

Table 1. Hemorrhage and mortality rates.

	PROACT II treatment	**PROACT II placebo**	**MERCI**
Mortality	25%	27%	38%*
Symptomatic ICH within 24 hours	10%	2%	8%**
Groin Hematoma	7%	17%	4%

* Mortality rate for MCA strokes (population studied in PROACT II) in MERCI was 32%

** Hemorrhage rate in MCA strokes in MERCI was 6%.

Primary Outcome Measures:

Out of 114 patients treated with the retriever, 54% (n=61) patients had TIMI grade II or III flow immediately post procedure. This is statistically significant compared to the placebo group in PROACT II (18% spontaneous revascularization in patients treated as randomized) with P <0.0001. It also is significantly greater than the target success rate of 30% revascularization. If all patients enrolled in the study are included (intent-to-treat success rate) the rate is 52% (62/120). Four patients who were successfully revascularized went on to have embolization of clot into a previously uninvolved territory (2 patients) or a symptomatic intracranial hemorrhage. Excluding these patients with serious adverse events, the study success rate (as defined as revascularization with the Retriever alone and without occurrence of serious adverse events) is 47% (57/120) Out of the 61 patients who had successful clot retrieval, 25% (15/61) went on to die prior to 90

day follow-up. In seventeen patients where the MERCI Retriever was unsuccessful in restoring flow, additional therapies were tried. Ten of these patients were successfully revascularized with another therapy, including 8 with IA thrombolysis and 2 with other mechanical devices

Secondary Outcome:
Secondary outcome measures included assessment of clinical outcome at 30 and 90 day follow-up. Modified Rankin scale scores and NIHSS scores were assessed at both of these end points. Thirty day follow-up is presented for 112 patients and 90 day follow-up for 70. Results are stratified by baseline NIHSS score due to the known association between poor outcomes and increasing baseline NIHSS (2). Comparisons are made to the clinical outcome results of the PROACT II trial, though important differences in the patient populations treated in PROACT II and MERCI make statistical comparisons less informative. One important difference between these two populations of patients is the severity of the strokes in the patients treated. Table 2 presents the distribution of baseline NIHSS scores in patients enrolled in MERCI as compared to the placebo group in the PROACT II study. As is evident from the table, a larger percentage of patients in the MERCI trial had NIHSS scores >20 as compared to PROACT II. Literature has shown that patients with baseline NIHSS >22 have a very poor prognosis with 98% experiencing poor outcome (3).

Table 2

Baseline NIHSS	MERCI	PROACT II placebo group
4-10*	3 (3%)	8 (14%)
11-20	62 (55%)	37 (63%)
>20**	48 (42%)	14 (23%)

* MERCI used 8 as the minimum NIHSS for enrolment
** Patients with NIHSS > 30 were excluded from PROACT II.

In PROACT II, a good outcome was defined as a mRS of = 2 at follow-up. Patients with mRS of = 2 can have a slight disability and may not be able to complete all previous activities, but are able to look after their own affairs without assistance. This is an appropriate cutoff point for a treatment of population of patients with more several strokes. Table 3 compares the rate of good outcome in the PROACT II treatment and placebo groups to all patients with 90 day data available in the MERCI trial. As has been stated previously, MERCI included both ICA strokes and posterior circulation strokes where was PROACT II enrollment was limited to only stroke in the MCA (M1 and M2 segments).

Table 3. Rate of good outcome at 90 day follow-up.

	PROACT II treatment		PROACT II control		MERCI	
NIHSS strata	**No.**	**mRS = 2**	**No.**	**mRS= 2**	**No.**	**mRS = 2**
< 10	16	10 (63%)	8	5(63%)	3	2(66%)
11-20	75	34 (45%)	37	9 (24%)	34	10 (29%)
>20	30	4 (13%)	14	1 (7%)	32	5 (16%)
Total	121	(40%)	59	(25%)	69	25%

The rate of good outcome (mRS = 2) in patients with MCA strokes (summing all baseline NIHSS scores) treated with the MERCI Retriever at 30 days was 24% (14/58). Patients with posterior circulation strokes faired much worse, having only 17% good outcome at 30 days. As Table 4 indicates, the treatment of MCA strokes in the MERCI trial showed no difference in clinical outcome compared to the PROACT II placebo group though the population treated in MERCI did have an increased severity of stroke at presentation.

Table 4

	MERCI MCA	**PROACT II placebo**
Baseline NIHSS median (range)	19 (9-40)	17 (4-28)
mRS < 3 at follow-up	14/58 (24%)	15/59 (25%)

While there was no difference in clinical outcome when comparing all of the patients treated in the MERCI trial to the outcomes of the PROACT II placebo group, a comparison of outcome in patients in whom there was successfully revascularization with the MERCI Retriever to those in whom the procedure was unsuccessful (including those that went on to successful revascularization with an alternative therapy as part of the unsuccessful group) demonstrated a clinical benefit to revascularization. Table 5 shows a comparison of the rate of good outcome (mRS = 2) at 90 days between patients with successful and unsuccessful revascularization stratified by baseline NIHSS. While the number of patients with 90 day follow-up available at the time of this review was small, a substantial difference between the outcome of patients with successful and unsuccessful revascularization is demonstrated. In particular, the effect in patients with more severe strokes at baseline is pronounced.

Table 5

Baseline NIHSS	**Successful Revascularization**		**Unsuccessful Revascularization**	
	Total patients	mRS = 2	Total patients	mRS = 2
8-10	2	100%	1	0%
11-20	16	56%	18	6%
>20	12	42%	20	0%

A comparison of all patients with successful revascularization to those without showed a significant increase in the likelihood of a poor outcome in those in whom flow was not restored (90% vs. 48%, P<0.001). The distribution of baseline NIHSS scores between

successful and unsuccessful populations was not statistically significantly different (p=0.575); indicating that severity of stroke was not correlated with difficulty in successfully completing the thrombectomy procedure.

Summary:
The MERCI trial data has been submitted to support a new indication for use for the legally marketed Concentric Retriever. This indication is to restore blood flow in the neurovasculature by removing thrombus in patients experiencing acute ischemic stroke. The primary endpoint of the study was to demonstrate successful revascularization of patients with an acceptable adverse event rate. The study demonstrated 47% successful revascularization of patients without occurrence of a serious adverse event, which was significantly different than the spontaneous revascularization rate of 18% seen in the placebo group of the PROACT II study.

The mortality rate, while higher than that seen in PROACT II, likely represents the expected mortality in the population treated, as the acuity of the stroke patients treated in the MERCI trial was higher. This is further confirmed by the low occurrence of device- and procedure-related serious adverse events (6%) and fatal device- and procedure-related adverse events (2%), indicating that the mortality rate is likely due to the natural history of patients with severe stroke and not a high rate of device or procedure related deaths. Similarly, the symptomatic intracranial hemorrhage rate of 8% seen in the MERCI trial is likely related to the inclusion of larger (ICA) strokes in the treatment group. The rate of hemorrhage in patients with MCA strokes was only 6%, half way between the 2% rate seen in the placebo group in PROACT II and the 10% rate seen in the PROACT II treatment group. The rate of 6% likely represents a combination of the 2 device related vessel injuries leading to subarachnoid hemorrhage and a slightly increased risk of hemorrhage in reperfused, injured brain.

The analysis of the clinical outcome of all patients treated in MERCI did not show a significant improvement over the outcome of patients in the PROACT II placebo group. Significant differences exist between these populations. As is shown in Table 1, the population studied in the MERCI trial had more severe strokes at presentation as compared to the population treated in PROACT II. Very few patients treated with the Retriever had NIHSS scores <11, a population whose expected outcome is quite good. As the trial was a single arm study and had different inclusion and exclusion criteria than PROACT II, the chosen control population, it was not deigned to demonstrate a clinical benefit of treatment. However, comparisons of the patients with successful revascularization to those in whom flow was not restored, and when stratified for baseline stroke severity, demonstrated better clinical outcomes are seen in patients in whom treatment was successful.

Michael J Schlosser, MD
Medical Officer
ODE/DGRND/GSBD

References:

1) Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F. "Intra-arterial prourokinase for Acute Ischemic Stroke. The PROACT II Study: A Randomized Controlled Trial." JAMA, 1999;282(21):2003-11.

2) H. P. Adams, P. H. Davis, E. C. Leira, K.-C. Chang, B. H. Bendixen, W. R. Clarke, R. F. Woolson, and M. D. Hansen. "Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST)" Neurology. 1999;53:126-31.

3) Frankel MR, Morgenstern LB, Kwiatkowski TG, Lu M, Tilley BC, Broderick JP, Libman R, Levine SR, and Brott T. "Predicting prognosis after stroke: A placebo group analysis from the National Institute of Neurological disorders and Stroke rt-PA Stroke Trial" Neurology 2000;55:952-959.

4) The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995 Dec 14;333(24):1581-7.

5) Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Hoxter G, Mahagne MH, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 1995 Oct 4;274(13):1017-25.

6) Del Zoppo GJ, Higashida RT, Furlan AJ, et al., PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. Stroke. 1998;29:4-11.

7) Donnan GA, Davis SM, Chambers BR, et al., Streptokinase for acute ischemic stroke with relationship to time of administration. JAMA 1996;276:961-966.

8) Leary MC, Saver JL, Gobin YP, et al., Beyond Tissue Plasminogen Activator: Mechanical Intervention in Acute Stroke. Ann Emerg Med. 2003;41:838-846.